Supplementary Information

Details of individual participating IBD cohorts

REMIND Network – Prospective cohort of CD patients (NCT03458195) included at time of ileocolonic resection, recruited in 15 centers from the REMIND network. Extensive biobanking at surgery and post-operative endoscopy. The aims are to identify predictors of post-operative endoscopic recurrence, and to better understand the pathophysiology of recurrence.

CCIM German cohort – Cohort was recruited through the Comprehensive Center for Inflammation Medicine (CCIM) of the University Hospital. Tertiary referral center with an IBD ambulance.

SPARC IBD – Study of a Prospective Adult Research Cohort with IBD – is a multicentered longitudinal study of adult IBD patients. The goal of the study is to find predictors of response to therapy and predictors of relapse that will lead to precision medicine strategies and new therapeutic targets that will improve the quality of life of patients with IBD. Data and biosamples are used for basic, clinical, and translational research.

Belgium IBD ULG – IBD clinics, Erasme hospital, Brussels, Belgium (2800 IBD patients, 650 patients on biologics) within the Belgium IBD Consortium together with the IBD clinical and research groups of ULG, ULB and ULiège.

The Miami cohort – made up of IBD patients from both an academic Crohn's and colitis referral center (the University of Miami Crohn's and Colitis Center) and a large, community-based practice (GastroHealth) in South Florida.

The MIRIAD Biorepository – Cedars-Sinai recruits adult and pediatric IBD patients who attend the IBD Centers at Cedars-Sinai as well as through collaborators across the world (particularly East Asia). Both adult and pediatric subjects are recruited and while the majority of subjects are of Northern European and Ashkenazi Jewish emphasis on African-American and Hispanic recruitment (the latter through a collaboration with the University of Puerto Rico).

The Nurses' Health Studies – NHS is among the largest prospective investigations into the risk factors for major chronic diseases in women.

FINRISK – The population-based FINRISK study has been followed up for IBD and other disease end-points using annual record linkage with the Finnish National Hospital Discharge Register, the National Causes-of-Death Register and the National Drug Reimbursement Register. Controls were chosen to have a high polygenic risk score for IBD without an IBD diagnosis. A detailed description of the FINRISK cohort can be found at Borodulin et al.

NIDDK IBD Genetics Consortium – The NIDDK Inflammatory Bowel Disease Genetics Consortium (IBDGC) was created in 2002 by the National Institute of Diabetes, Digestive and Kidney diseases (NIDDK) to advance knowledge on the inflammatory bowel diseases, specifically Crohn's Disease and Ulcerative Colitis. The Consortium consists of six genetic research centers (GRC) and a data coordinating center (DCC) that prospectively recruits a combination of cases, controls, and trios to gather a large collection of samples and linked phenotype information. DNA samples are used to conduct genetic linkage and association studies. For more information please see https://ibdgc.org/

NIDDK-Quebec – a cohort of Crohn's disease patients, and healthy controls (spouses and/or "best friend") recruited in the Province of Quebec, Canada as part of the activities of the Montreal-Boston Genetic Research Center (GRC, Rioux is PI), one of six GRCs of the NIDDK-funded IBD Genetics Consortium (https://ibdgc.uchicago.edu/grc/montreal/). Patients and controls were recruited at university-based hospitals throughout the province by gastroenterologists specializing in IBD that formed the Quebec IBD Genetics Consortium. For more information please see https://www.medgeni.org/projects/qibdgc

Genome Quebec-GENIZON – a cohort of Crohn's disease patients, and healthy controls, of French Canadian origin recruited in the Province of Quebec, Canada. Previously collected by Genizon Biosciences Inc. but now part of a public biobank overseen by Génome Québec. For more information please visit: https://www.genomequebec.com/genizon-biobank/

Belgium IBD Leuven center – a tertiary referral center for IBD. Annually 3.000 patients are followed up in the clinic (2/3 are CD and 1/3 is UC). Patients are recruited via the IBD clinic to participate in the research on IBD by providing biomaterials and clinical data, stored in the electronic clinical records (KWS or Clinical Working Station) to the IBD Biobank (CCare, PI: Séverine Vermeire, EC approval). Controls are also recruited into CCare as healthy spouses of the included patients and through advertisements on campus. IBD Leuven is part of the Belgian IBD Genetics Consortium, together with the IBD clinical and research groups of ULG, ULB and ULiège.

MGH Pediatric Inflammatory Bowel Disease Center – a collection that provides care for children and adolescents with inflammatory bowel diseases (ulcerative colitis, indeterminate colitis, and crohn's disease).

PRISM (Prospective Registry in IBD Study at MGH) – a registry that includes more than 3,000 enrolled IBD patients and healthy controlled individuals.

SHARE – Investigators from seven major IBD centers formed the Sinai Helmsley Alliance for Research Excellence (SHARE) in 2010 to integrate information from basic science, epidemiology and information sciences to advance IBD research across multiple high-volume centers.

Epi25 Controls – is a collaboration of more than 200 partners from over 50 research cohorts from around the world to investigate the genetics of epilepsy. Whole exome sequencing data from the following Epi25 cohorts were included in these analyses: Germany: Bonn; Germany: Kiel; Germany: Tuebingen; Germany: Leipzig; Ireland: Dublin; USA: Philadelphia/CHOP; USA: EPGP; USA: Human Epilepsy Project; and USA: Penn/CHOP. Detailed descriptions of the cohorts, study PIs and teams, and local acknowledgements can be found in Epi25 Collaborative, AJHG, 2021. (https://pubmed.ncbi.nlm.nih.gov/33932343/)

UK-IRL-UCL Controls – samples were extracted from EBV transformed peripheral blood lymphocytes from unscreened healthy British blood donors and from whole blood samples from healthy volunteers of UK or Irish ancestry.

MIGEN-Leicester Controls – cases were ascertained from two studies: (i) the British Heart Foundation Family Heart Study and (ii) the BRICCS Study. Control subjects were ascertained from the control subjects being recruited as part of the UK Aneurysm Growth Study (UKAGS). All exome sequencing was performed at the Broad Institute of Harvard and MIT; sample sequence capture was performed using Illumina's ICE Capture reagent and sequencing was performed on an Illumina HiSeq 2000 or 2500.

MIGEN-Ottawa Controls – The Ottawa Heart Study is a cross-sectional case-control study designed to identify genes that predispose to angiographically defined coronary artery disease. All exome sequencing was performed at the Broad Institute of Harvard and MIT; sample sequence capture was performed using Agilent SureSelect Human All Exon Kit v2 and sequencing was performed on an Illumina HiSeg 2000 or 2500.

ASC-NIMH Controls – The ARRA Autism Sequencing Collaboration was created in 2010 bringing together an expert large-scale sequencing center and a collaborative network of research labs focused on the genetics of autism. These groups worked together to utilize dramatic new advances in DNA sequencing technology to reveal the genetic architecture of autism through comprehensive examination of the exotic sequence of all genes. The Autism Sequencing Consortium (ASC) was founded by Joseph D. Buxbaum and colleagues as an international group of scientists who share autism spectrum disorder (ASD) samples and genetic data.

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- ¹²⁵Chelsea and Westminster Hospital NHS Foundation Trust West Middlesex University Hospital, UK
- ¹²⁶Maidstone & Tunbridge Wells NHS Trust Maidstone Hospital, UK
- ¹²⁷Portsmouth Hospitals NHS Trust Queen Alexandra Hospital, Portsmouth, UK
- ¹²⁸James Paget University Hospitals NHS Foundation Trust James Paget University Hospital, UK
- 129 Gateshead Health NHS Foundation Trust Queen Elizabeth Hospital, UK
- ¹³⁰Royal Cornwall Hospitals NHS Trust Royal Cornwall Hospital, UK
- ¹³¹North Tees and Hartlepool NHS Foundation Trust University Hospital of North Tees, UK
- ¹³²University College London Hospitals NHS Foundation Trust University College Hospital, UK
- ¹³³Princess Alexandra Hospital NHS Trust Princess Alexandra Hospital, UK
- ¹³⁴East and North Hertfordshire NHS Trust Lister Hospital, UK
- ¹³⁵North West Anglia NHS Foundation Trust Peterborough City Hospital, UK
- ¹³⁶Shrewsbury and Telford Hospital NHS Trust Royal Shrewsbury Hospital, UK
- ¹³⁷St Helens and Knowsley Teaching Hospitals NHS Trust Whiston Hospital, UK
- ¹³⁸University Hospitals of Derby and Burton NHS Foundation Trust Royal Derby Hospital, UK
- ¹³⁹East Lancashire Hospitals NHS Trust Royal Blackburn Hospital, UK
- ¹⁴⁰University Hospital Southampton NHS Foundation Trust Southampton General Hospital, UK
- ¹⁴¹University Hospitals of Morecambe Bay NHS Foundation Trust Furness General Hospital, UK
- ¹⁴²University Hospitals of Leicester NHS Trust Leicester General Hospital, UK
- ¹⁴³Royal Berkshire NHS Foundation Trust Royal Berkshire Hospital, UK
- ¹⁴⁴Sherwood Forest Hospitals NHS Foundation Trust King's Mill Hospital, UK
- ¹⁴⁵Ashford & St Peter's Hospitals NHS Foundation Trust Ashford Hospital, UK
- ¹⁴⁶Manchester University NHS Foundation Trust Wythenshawe Hospital, UK
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- ¹⁵⁰Western Sussex Hospitals NHS Foundation Trust Worthing Hospital & St Richard's Hospital, UK
- ¹⁵¹Basildon & Thurrock University Hospitals NHS Foundation Trust Basildon University Hospital, UK
- ¹⁵²Bedford Hospital NHS Trust Bedford General Hospital, UK
- ¹⁵³Luton and Dunstable University Hospital NHS Foundation Trust Luton and Dunstable University Hospital, UK
- ¹⁵⁴North West Anglia NHS Foundation Trust Hinchingbrooke Hospital, UK
- ¹⁵⁵Royal Devon & Exeter NHS Foundation Trust Royal Devon and Exeter Hospital, UK
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- ¹⁵⁸East Cheshire NHS Trust Macclesfield District General Hospital, UK
- ¹⁵⁹Milton Keynes University NHS Foundation Trust Milton Keynes University Hospital, UK
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- ¹⁶¹NHS Lothian Western General Hospital, UK
- ¹⁶²University Hospitals Plymouth NHS Trust Derriford Hospital, UK
- ¹⁶³Pennine Acute Hospitals NHS Trust Fairfield General Hospital, UK
- 164Sheffield Teaching Hospitals NHS Foundation Trust Royal Hallamshire Hospital, UK
- ¹⁶⁵Salisbury NHS Foundation Trust Salisbury District Hospital, UK
- ¹⁶⁶North Cumbria Integrated Care NHS Foundation Trust Cumberland Infirmary Hospital, UK
- ¹⁶⁷Salford Royal NHS Foundation Trust Salford Royal Hospital, UK
- ¹⁶⁸Royal Bournemouth & Christchurch Hospitals NHS Foundation Trust Royal Bournemouth Hospital, UK
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- ¹⁷¹York Teaching Hospital NHS Foundation Trust Scarborough Hospital, UK
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- ¹⁷⁵Mid Essex Hospital Services NHS Trust Broomfield Hospital, UK
- ¹⁷⁶Buckinghamshire Healthcare NHS Trust Wycombe Hospital, UK
- ¹⁷⁷Chesterfield Royal Hospital NHS Foundation Trust Chesterfield Royal Hospital, UK
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- ¹⁸⁰Surrey and Sussex Healthcare NHS Trust East Surrey Hospital, UK
- ¹⁸¹South Tees Hospitals NHS Foundation Trust James Cook University Hospital, UK
- ¹⁸²Hampshire Hospitals NHS Foundation Trust Basingstoke and North Hampshire Hospital, UK
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- ¹⁹⁴Yeovil District Hospital NHS Foundation Trust Yeovil District Hospital, UK
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- ¹⁹⁶Wrightington, Wigan & Leigh NHS Foundation Trust Royal Albert Edward Infirmary, UK
- ¹⁹⁷Royal Wolverhampton NHS Trust New Cross Hospital, UK
- ¹⁹⁸Liverpool University Hospitals NHS Foundation Trust Royal Liverpool and Broadgreen University Hospital, UK
- ¹⁹⁹Northern Devon Healthcare NHS Trust North Devon District Hospital, UK
- ²⁰⁰East Sussex Healthcare NHS Trust Eastbourne District General Hospital, UK
- ²⁰¹Weston Area Health NHS Trust Weston General Hospital, UK
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- ²⁰³Mid Yorkshire Hospitals NHS Trust Pinderfields General Hospital, UK
- ²⁰⁴Kettering General Hospital NHS Foundation Trust Kettering General Hospital, UK
- ²⁰⁵Torbay and South Devon NHS Foundation Trust Torbay Hospital, UK
- ²⁰⁶Kingston Hospital NHS Foundation Trust Kingston Hospital, UK
- ²⁰⁷Taunton & Somerset NHS Foundation Trust Musgrove Park Hospital, UK

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